REMARKS

Claims 21-40 are pending. Claims 34-40 were previously withdrawn from consideration as being directed to a non-elected invention. Claims 21-33 are under examination. Claims 25, 26, 28-30 are hereby canceled without prejudice. Claims 21-24, 27, and 31-33 are hereby amended. Support for the claim amendments can be found throughout the originally filed Specification and originally filed claims.

No new matter is introduced by the amendments.

After entry of the present Amendments, Claims 21-24, 27, and 31-33 will be pending for examination.

Response to Objection under 37 CFR 1.821-1.825

The Office Action states that the present application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because a sequence in FIG. 3 is not identified by a SEQ ID NO. and that insertion of the SEQ ID NO. of the sequence in the description of FIG. 3 in the Brief Description of the Drawings would obviate this objection.

Applicants hereby amend the Specification to insert SEQ ID NO. 58 in para. [0021] and submit that the amendment overcomes the instant objection.

Reconsideration and withdrawal of the instant rejection is respectfully requested.

Response to Claim Rejections – 35 USC §112

The Office Action has rejected Claims 21-23 and 33 under 35 U.S.C. §112, first paragraph. The Office Action states that the Specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. More particularly, the Office Action

states that the Specification does not reasonably provide enablement for a single chain tri-specific antibody comprising an anti-tumor associated antigen antibody fragment, an anti-CD3 antibody fragment and an anti-CD28 antibody fragment.

Without acquiescing to the Office Action and in an effort to advance the prosecution of the instant Application, Applicants have canceled Claims 25, 26, and 28-30 and amended Claims 21-24, 27, and 31-33. Applicants submit that the instant amendments place the claims within a scope well enabled and supported by the Specification as filed and meet the requirements of 35 U.S.C. 112, first paragraph.

Reconsideration and withdrawal of the instant rejection is respectfully requested.

Response to Claim Rejections – 35 USC §102(b)

The Office Action has rejected Claims 21-24, 26, 28-31, and 33 under 35 U.S.C. §102(b), as allegedly being anticipated by Song, *et al.* **2003** *Acta Biochimica Biophysica Sinica* 35:503-510 (herein referred to as the "*Song et al.*").

The Office Action has also rejected Claims 21-24, 26, 28-31, and 33 under 35 U.S.C. §102(b), as allegedly being anticipated by WO 02/83738 by Huang, *et al.* (as evidence by the national stage US Application Publ. No. 2005/0175606).

The Office Action states that each of *Song et al.* and WO 02/83738 discloses a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment and that *Song et al.*'s single chain tri-specific antibody comprises a C myc tag and two interlinkers, an interlinker-Fc and in interlinker-HAS.

Without acquiescing to the Office Action and in an effort to advance the prosecution of the instant Application, Applicants have canceled Claims 25, 26, and 28-30 and amended Claims 21-24, 27, and 31-33.

Applicants submit that neither *Song et al.* nor WO 02/83738 discloses a linear single chain recombinant tri-specific antibody scTsAb comprising in tandem an anti-Carcinoma-Embryonic Antigen single chain antibody fragment of a variable region (scFv) of the tri-specific antibody, an Fc linking peptide, an anti-CD3 single chain antibody fragment of the variable region (scFv), a human serum albumin linking peptide, and an anti-CD28 single-domain antibody fragment.

Therefore, it is respectfully submitted that amended Claim 21 is patentable under 35 U.S.C. §102(b) over *Song et al.* and WO 02/83738. Amended Claims 22-24, 27, and 31-33, being dependent from Claim 21, are patentable over *Song et al.* and WO 02/83738 under 35 U.S.C. §102(b).

Reconsideration and withdrawal of the instant rejection is respectfully requested.

Response to Claim Rejections – 35 USC §103(a)

The Office Action has rejected Claims 21-26, 28-31 and 33 under 35 U.S.C. §103(a), as allegedly being unpatentable over *Song et al.* in view of Holliger, *et al.* **1999** *Cancer Res.* 59:2909-2916 (herein referred to as the "*Holliger et al.*").

The Office Action states that *Song et al.* does not disclose a single chain tri-specific antibody comprising in tandem an anti-CEA antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second linker and a n anti-CD28 antibody fragment. The Office Action further states that *Holliger et al.* discloses two bispecific antibodies, an anti CEA X anti-CD3 antibody and an anti-CEA X B7 fusion protein. And it would have been *prima facie* obvious to combine *Song et al.* and *Holliger et al.*

Without acquiescing to the Office Action and in an effort to advance the prosecution of the instant Application, Applicants have canceled Claims 25, 26, and 28-30 and amended Claims 21-24, 27, and 31-33.

The vectors pTRI and psTRI disclosed in *Song et al.* encode for a trispecific antibody carrying Fc hinges at both ends. On protein level these constitute cysteine-rich structures, which in vivo form intra- and intermolecular disulfide bonds. Hence, the trispecific antibodies disclosed in *Song et al.* either form circular antibodies by intramolecular disulfide bonds and are thus not linear or form polymeric antibodies by intermolecular disulfide bonds that are not single-chain antibodies.

In contrast, amended claims recite linear single-chain recombinant trispecific antibody. *Holliger et al.* does not cure the deficiencies of *Song et al.* because it does not contain any suggestion to modify the preparative methods of antibodies according to *Song et al.* such that the single-chain tri-specific antibodies of *Song et al.* become linear.

Thus, Applicants submit that *Song et al.* and *Holliger et al.*, individually or in combination, do not disclose a linear single chain recombinant tri-specific antibody scTsAb comprising in tandem an anti-Carcinoma-Embryonic Antigen single chain antibody fragment of a variable region (scFv) of the tri-specific antibody, an Fc linking peptide, an anti-CD3 single chain antibody fragment of the variable region (scFv), a human serum albumin linking peptide, and an anti-CD28 single-domain antibody fragment.

Therefore, it is respectfully submitted that amended Claim 21 is patentable under 35 U.S.C. §103(a) over *Song et al.* and *Holliger et al.*, individually or in combination. Amended Claims 22-24, 27, and 31-33, being dependent from Claim 21, are patentable over *Song et al.* and *Holliger et al.* under 35 U.S.C. §103(a).

The Office Action also has rejected Claims 21-33 under 35 U.S.C. §103(a), as allegedly being unpatentable over *Song et al.* in view of *Holliger et al.* and in further view of Koga, *et al.* **1990** *Hybridoma* 9:43-56 (hereinafter "*Koga et al.*") and US Patent No. 5,618,920 by Robinson *et al.*

The Office Action states that neither *Song et al.* nor *Holliger et al.* disclose an anti-CEA antigen binding fragment comprising SEQ ID NO:1. The Office Action states *Koga et al.* disclose the anti-CEA monoclonal antibody that was used to make the anti-CEA scFv. And *Robinson et al.* disclose the determination of nucleic acids encoding VH and VL of any known antibody and use of the VH and VL to produce FV. The Office Action concludes that one of ordinary skill in the art would have been motivated to apply *Robinson et al.*'s method of determination of nucleic acids encoding VH and VL of an antibody to Koga et al.'s anti-CEA antibody, and then motivated to combine with *Song et al.* and *Holliger et al.*'s single chain tri-specific antibody.

Applicants submit that the deficiencies of *Song et al.* are not cured by *Holliger et al.*, *Koga et al.* and *Robinson et al.*, which individually or collectively remain insufficient in providing enabling disclosure that teach or suggest Claim 21 as amended. As discussed before, the tri-specific antibodies disclosed in *Song et al.* either form circular antibodies by intramolecular disulfide bonds and are thus not linear or form polymeric antibodies by intermolecular disulfide bonds that are not single-chain antibodies. *Holliger et al.* does not cure the deficiencies of *Song et al.* because it does not contain any suggestion to modify the preparative methods of antibodies according to *Song et al.* such that the single-chain tri-specific antibodies of *Song et al.* become linear. *Koga et al.* and *Robinson et al.* are similarly lacking in addressing this aspect of the claimed invention.

Therefore, it is respectfully submitted that amended Claim 21 is patentable under 35 U.S.C. §103(a) over *Song et al.* in view of *Holliger et al.* and in further view of *Koga et al.* and Robinson *et al.* Amended Claims 22-24, 27, and 31-33, being dependent from Claim 21, are patentable over *Song et al.* in view of *Holliger et al.* and in further view of *Koga et al.* and Robinson *et al.* under 35 U.S.C. §103(a).

Reconsideration and withdrawal of the instant rejection is respectfully requested.

CONCLUSION

Applicants respectfully request that the application be reconsidered and that the pending rejections be withdrawn. Applicants submit that all claims pending are now in proper condition for allowance, and request the issuance of a Notice of Allowance at the Examiner's earliest convenience.

If the Examiner believes that contact with Applicants' attorney would be advantageous toward the disposition of this case, the Examiner is encouraged to call the undersigned at the phone number noted below.

Respectfully submitted,
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